FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

DIFLUBENZURON

1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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[1] This disclaimer applies to all specifications published by FAO.

INTRODUCTION

FAO establishes and publishes specifications* for technical material and related formulations of agricultural pesticides, with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

Since 1999 the development of FAO specifications follows the **New Procedure**, described in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products" (FAO Plant Production and Protection Page No. 149). This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPS, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 2000 onwards the publication of FAO specifications under the **New Procedure** has changed. Every specification consists now of two parts namely the specifications and the evaluation report(s):

PART ONE: **The Specification** of the technical material and the related formulations of the plant protection product in accordance with chapter 4, 5 and 6 of the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products".

PART TWO: **The Evaluation Report(s)** of the plant protection product reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are to be provided by the manufacturer(s) according to the requirements of Appendix A, annex 1 or 2 of the "Manual on the development and use of FAO specifications for plant protection products" and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

FAO specifications under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. FAO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (http://www.fao.org/ag/agp/agpp/pesticid/)

OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

DIFLUBENZURON

DIFLUBENZURON

INFORMATION

ISO common name

Diflubenzuron (E-ISO, (m) F-ISO, ANSI, ESA)

Chemical names

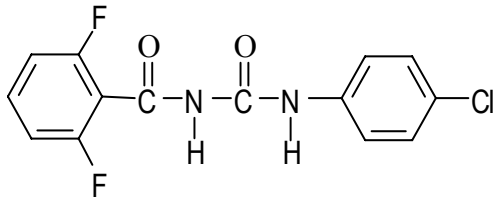
IUPAC: 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea

CAS: *N*-[[(4-chlorophenyl)amino]carbonyl]-2,6-difluorobenzamide

Synonyms

Dimilin, Micromite, Adept, Du-Dim, Device, DU 112307, PH 60-40, TH 6040, ENT-29054, OMS 1804 (Crompton trade names and/or past development codes).

Structural formula



Molecular formula

$C_{14}H_9ClF_2N_2O_2$

Relative molecular mass

310.7

CAS Registry number

35367-38-5

CIPAC number

339

Identity tests

HPLC retention time; IR spectrum

DIFLUBENZURON TECHNICAL CONCENTRATE

FAO specification 339/TK (May 2005*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (*339/2004*). It should be applicable to relevant products of these manufacturers but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation report (*339/2004*) as PART TWO forms an integral part of this publication.*

1 Description

The material shall consist of diflubenzuron, together with related manufacturing impurities, and shall be an off-white, fine powder, free from visible extraneous matter and added modifying agents except for the diluent.

2 Active ingredient

2.1 **Identity tests** (CIPAC method 339/TK/M/2, Handbook H, p.141, 1998)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Diflubenzuron content** (CIPAC method 339/TK/M/3, Handbook H, pp.141-144, 1998)

The diflubenzuron content shall be declared (not less than 900 g/kg) and, when determined, the average measured content shall not differ from that declared by more than ± 25 g/kg.

3 Physical properties

3.1 **Particle size** (MT 187, CIPAC Handbook K, p.153, 2003) (Note 1)

Particles smaller than 5 µm: not less than 70% w/w.

Average particle size: not more than 3.75 µm.

Note 1 Control of particle size is required to ensure efficacy of the formulated products.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/ag/agp/agpp/pesticid/.

PART TWO

EVALUATION REPORTS

DIFLUBENZURON

DIFLUBENZURON
FAO/WHO EVALUATION REPORT 339/2004

Explanation

The data for diflubenzuron were evaluated in support of review of existing WHO specifications, WHO/SIT/25.R1 for diflubenzuron technical concentrate (TK) and WHO/SIF/47.R1 for diflubenzuron wettable powder (WP), as developed by WHOPES following the old procedure and revised on 10 December 1999. New specifications were proposed for diflubenzuron granules (GR) and tablets for direct application (DT) in public health and for suspension concentrates (SC) for use in agriculture.

Diflubenzuron is not under patent.

Diflubenzuron was evaluated by the FAO/WHO JMPR and WHO/IPCS in 1981, 1984, 1988 and 2002. The US EPA published a Re-registration Eligibility Decision for diflubenzuron in August 1997. Diflubenzuron is currently under review by the European Commission under Directive 91/414/EC. Crompton Europe B.V. has notified diflubenzuron as an existing biocidal active ingredient under the Biocidal Products Directive 98/8/EC.

The draft specification and the supporting data were provided by Crompton Europe B.V. in October 2003 and February 2004.

Uses

Diflubenzuron is an insect growth regulator, used in agriculture, horticulture and forestry against larvae of Lepidoptera, Coleoptera, Diptera, Hymenoptera and in public health against larvae of mosquitoes and other noxious insects.

Identity

ISO common name

Diflubenzuron (E-ISO, (m) F-ISO, ANSI, ESA)

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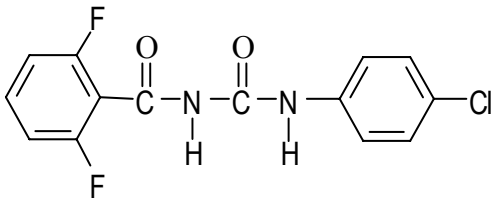

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Relative molecular mass

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CAS Registry number

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Identity tests

HPLC retention time; IR spectrum.

Physical and chemical properties

Table 1. Physicochemical properties of pure diflubenzuron

Characteristic	Value	Purity, %	Method	Reference
Vapour pressure	≤1.2 x 10^{-7} Pa at 25°C	>99.5	OECD guideline 104	Harteveld, 1988
Melting point, boiling point and/or temperature of decomposition	Melting point: 228°C Boiling point: Not required, because diflubenzuron is neither a liquid, nor a low melting substance Decomposition temperature: no decomposition at melting point	99.9	OECD guideline 102	Thus et al 1995 Riggs 1999 Thus et al 1995
Solubility in water	0.08 mg/l at 25°C at pH 7 0.10 mg/l at pH 4 0.32 mg/l at pH 10	>99.5	EEC guideline A6	Balder et al 1989 Kempen et al 1995
Octanol/water partition coefficient	Log P_{OW} = 3.89 at 22°C at pH 3	99.9	EEC guideline A8	Thus 1988
Hydrolysis characteristics	Half-life > 180 days at 25°C at pH 5 and 7 Half-life = 32.5 days at 25°C at pH 9	97.1	EPA guideline CG5000	Boelhouwers et al 1988
Photolysis characteristics	The estimated half-life of diflubenzuron in natural sunlight at latitude 40° N is 80 days at 25°C (from 40 days continuous irradiation with a 450 W Xenon arc lamp)	97.1	EPA guideline CG6000	Boelhouwers et al 1988 Voorden 1993
Dissociation characteristics	Does not dissociate	99.9	OECD guideline 112	Yu 1999

Table 2. Chemical composition and properties of diflubenzuron technical concentrate (TK)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data.	Confidential information supplied and held on file by FAO. Mass balances were 99.0-100.3%.
Declared minimum diflubenzuron content:	875 g/kg
Relevant impurities ≥1 g/kg and maximum limits for them:	None *
Relevant impurities <1 g/kg and maximum limits for them:	None
Stabilizers or other additives and maximum limits for them:	None
Melting or boiling temperature range	228°C, no decomposition at melting point.
Particle size	Particles smaller than 5 µm: not less than 70% w/w. Average particle size: not more than 3.75 µm.

* Water is a relevant impurity in GR (20 g/kg) and DT (40 g/kg), because these formulations contain effervescent systems.

Hazard summary

Notes.

(i) The proposers provided written confirmation that the toxicological and ecotoxicological data included in the summary below were derived from diflubenzuron having impurity profiles similar to those referred to in the table above.

(ii) The conclusions expressed in the summary below are those of the proposers, unless otherwise specified.

(iii) The acute toxicity data relate to studies with diflubenzuron TC and/or with diflubenzuron VC-90, a TK containing 90% diflubenzuron, which has the same toxicological profile as the active ingredient itself.

Table 3. Toxicology profile of technical diflubenzuron, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions	Result	Reference
Rat (male and female)	Oral	OECD guideline 401, purity 90%	LD_{50} >5000 mg/kg bw	Koopman 1984a
Rat; mouse (male and female)	Oral (gavage)	Guideline not stated, purity 99.6%	LD_{50} >4640 mg/kg bw	Eldik, van 1973
Mouse (male and female)	Oral (gavage)	Guideline not stated, purity 99.6%	LD_{50} >4640 mg/kg bw	Koopman 1977
Rat (male and female)	Dermal	OECD guideline 402, purity 90%	LD_{50} >2000 mg/kg bw	Koopman 1984b
Rat	Dermal	24 hours. PSD, UK (1971) purity 99.6%	LD_{50} >10000 mg/kg bw	Keet 1976
Rat (male and female)	Inhalation	OECD guideline 403 purity 90%	LC_{50} >2490 mg/m^3	Greenough and McDonald 1986
Rat	Inhalation	Guideline not stated, purity 99.6%	LC_{50} >2900 mg/m^3	Berczy *et al*. 1973
Rabbit (male and female)	Skin irritation	OECD guideline 404, purity 90%	Non-irritant	Koopman 1984c

Species	Test	Duration and conditions	Result	Reference
Rabbit (male and female)	Eye irritation	OECD guideline 405, purity 90%	Slightly irritating (Note 1)	Koopman 1984d
Guinea pig	Skin sensitization	OECD guideline 406, purity 95.6%	Non-sensitizer	Prinsen 1992

Note 1: Although a slight reaction was observed during the eye irritation tests, the findings did not trigger classification of diflubenzuron as an eye irritant.

Table 4. Toxicology profile of technical diflubenzuron based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions	Result	Reference
Mouse	Oral 6-week	No guideline specified, Dose range tested: 0; 16 & 50 ppm; purity 99.6%	NOAEL = 2.0 mg/kg bw/day (16 ppm)	Hunter *et al*. 1974 DI-3523
Mouse	Oral 90-day	No guideline specified, Dose range tested: 0; 16; 50; 400; 2,000; 10,000 & 50,000 ppm; purity 97.2%	NOAEL = 7.1 mg/kg bw/day (50 ppm)	Burdock *et al*., 1980a DI-2212 Goodman 1980a DI-3522
Mouse	Oral 14-week	No guideline specified, Dose range tested: 0; 80; 400; 2000; 10,000 & 50,000 ppm; purity 97.2%	NOAEL = 10.4 mg/kg bw/day (80 ppm)	Colley *et al*., 1981 DI-4155
Rat	Oral 28-day	No guideline specified, dose range tested: 0; 800; 4,000; 20,000 & 100,000 ppm; purity 98.5%.	LOEL = 84 mg/kg bw/day (800 ppm)	Palmer *et al*., 1977 DI-4161
Rat	Oral 90-day	No guideline specified, dose range tested: 0; 3.125; 12.5; 50 & 200 ppm; purity 96.0%.	NOAEL = 21.6 mg/kg bw/day (200 ppm)	Kemp *et al*., 1973a,b DI-2376; Offringa, 1977 DI-3528
Rat	Oral 90-day	No guideline specified, Dose range tested: 0; 160; 400; 2,000; 10,000 & 50,000 ppm; purity 96.0%	NOAEL = 12.6 mg/kg bw/day (160 ppm)	Burdock *et al*., 1980b DI-2168; Goodman, 1980b DI-4279
Rat	Oral 9-week	No guideline specified; Dose range tested: 0; 10,000 & 100,000 ppm; purity 98.5%	LOEL = 1000 mg/kg bw/day (10.000 ppm)	Hunter *et al*. 1979 DI-3517
Dog	Oral 90-day	No guideline specified, Dose range tested: 0; 10; 20; 40 & 160 ppm; purity 99.6%	NOAEL = 0.84 mg/kg bw/day (20 ppm)	Chesterman *et al*., 1974 DI-2375
Dog	Oral 90-day	No guideline specified, Dose range tested: 0; 2; 4; 50 &; 250 mg/kg bw/day; purity 97.6%	NOAEL = 4 mg/kg b.w./day	Versendaal *et al*., 1983 DI-987
Dog	Oral 1-year	No guideline specified, Dose range tested: 0; 2; 10; 50 & 500 mg/kg b.w./day; purity 97.6%	NOAEL = 2 mg/kg b.w./day	Greenough *et al*., 1985 DI-4852

Species	Test	Duration and conditions	Result	Reference
Rat	Inhalation 28-day (1 hr/day)	No guideline specified, Dose range tested: 0; 0.5/0.12; 5.0/0.87 & 50/1.85 mg/L (nominal/actual); purity: 99.6%	NOAEL = 0.12 mg/L (actual)	Berczy *et al*. 1975a DI-2359
Rabbit	Inhalation 21-day (1 hr/day)	No guideline specified, Dose range tested: 0; 0.5/0.15; 5.0/0.75; 25/1.79 mg/L (nominal/actual); purity 99.6%	NOAEL = 0.15 mg/L (actual)	Berczy *et al*., 1975b DI-2357
Rat	Inhalation 28-day (6 hr/day)	OECD Guideline 412; Dose range tested: 0; 10/12; 30/34 & 100/109 mg/m^3 (nominal/actual); purity 96.5%	NOAEL = 34 mg/m^3 (actual)	Newton, 1999 DI-11497
Rabbit	Percutaneous 21-day	No guideline specified, Dose range tested: 0; 69.6; 150 & 322.5 mg/kg/day; purity 99.6%	NOAEL = 150 mg/kg/day	Davies *et al*., 1975a DI-2216
Rabbit	Percutaneous 21-day	No guideline specified, Dose range tested: 0; 113 & 345 mg/kg/day; purity 99.6%	Not established	Davies *et al*., 1975b DI-2217
Rat	Percutaneous 21-day	Guideline US EPA FIFRA vol 43, no 163, Dose range tested: 0; 20; 500 & 1,000 mg/kg/day; purity 96.7%	NOAEL = 20 mg/kg/day	Goldenthal, 1996 DI-9429
Rat	104 weeks dietary carcinogenicity	No guideline specified; Dose range tested: 0; 10; 20; 40; and 160 ppm; purity 99.6%	NOAEL = 1.43 mg/kg bw (males) and 1.73 mg/kg bw (females) (40 ppm) Not carcinogenic	Hunter *et al*. 1976 DI-4037
Rat	104 weeks dietary carcinogenicity	Guideline US EPA FIFRA vol. 43 no. 163; Dose range tested: 0; 156; 625; 2,500 and 10,000 ppm; purity 97.6%	LOAEL = 7.8 mg/kg bw/day (156 ppm) Not carcinogenic	Burdock *et al*., 1984 DI-8147
Mouse	80 weeks dietary carcinogenicity	No guideline specified; Dose range tested: 0; 4; 8; 16 and 50 ppm; purity: 99.6%	> 7.4 mg/kg bw/day (> 50 ppm) Not carcinogenic	Hunter *et al*., 1975 DI-3525, DI-3526 & DI-3527
Mouse	91 weeks dietary carcinogenicity	No guideline specified; Dose range tested: 0; 16; 80; 400; 2,000 and 10,000 ppm; purity 97.6%.	NOAEL = 2.4 mg/kg bw/day (16 ppm) Not carcinogenic	Colley *et al*., 1984 DI-8146
Rat	3-generation parental and reproduction toxicity	No guideline specified; Dose range tested: 0, 10, 20, 40 and 160 ppm; purity 99.6%	NOAEL = 8 mg/kg bw/day (160 ppm)	Palmer & Hill, 1975a DI-3516

Species	Test	Duration and conditions	Result	Reference
Rat	1-generation reproduction toxicity	No guideline specified; Dose range tested: 0, 1000 and 100000 ppm; purity 98.5%	NOAEL = 50 mg/kg bw/day (1000 ppm)	Palmer *et al*., 1978 DI-3462
Rat	2-generation reproduction toxicity	OECD guideline 416; Dose range tested: 0, 500, 5000 and 50000 ppm; purity 97.1%	NOAEL for reproductive function = 2500 mg/kg bw/day (50000 ppm)	Brooker 1995a,b DI-9182
Rat	Teratogenicity (gavage)	No guideline specified; Dose range tested: 0, 1,2 and 4 mg/kg bw during days 6-15 of gestation; purity 98.5%	Pregnancy rates were unaffected	Palmer & Hill, 1975b DI-2349
Rat	Teratogenicity (gavage)	US EPA guideline 83-3 subdivision F; Dose range tested: 0 and 1000 mg/kg bw during days 6-15 of gestation; purity 98.5%	No maternal or embryotoxicity at 1000 mg/kg bw/day	Kavanagh, 1987 DI-6552
Rabbit	Teratogenicity (gavage)	No guideline specified; Dose range tested: 0, 1,2 and 4 mg/kg bw during days 6-19 of gestation; purity 98.5%	Pregnancy rates were unaffected	Palmer & Hill, 1975c DI-2350
Rabbit	Teratogenicity (gavage)	US EPA guideline 83-3 subdivision F; Dose range tested: 0 and 1000 mg/kg bw during days 7-19 of pregnancy; purity 98.5%	NOAEL for maternal and embryotoxicity = 1000 mg/kg bw/day	Kavanagh, 1987b DI-6553

a Highest dose tested.
b Lowest dose tested.

Table 5. Mutagenicity profile of technical diflubenzuron based on *in vitro* and *in vivo* tests.

Species	Test	Conditions	Result	Reference
Salmonella typhimurium	*In vitro* genotoxicity test	OECD guideline 471, purity 96.9%	Negative	Koorn 1990
Saccharomyces cerevisiae	*In vitro* genotoxicity test	OECD guideline 471, purity 98.5%	Negative	Brusick & Weir 1977a
BALB/3T3 cells	*In vitro* genotoxicity test	OECD guideline 471, purity 98.5%	Negative	Brusick & Weir 1977b
CHO cells	*In vitro* genotoxicity test	OECD guideline 473, purity 97.6%	Negative	Taalman and Hoorn 1986
Rat hepatocytes	*In vivo* genotoxicity test	OECD guideline 482, purity 96.9%	Negative	Enninga 1990
WI-38	*In vivo* genotoxicity test	OECD guideline 486, purity 98.5%	Negative	Brusick & Weir 1977c
Mouse germ cells	Dominant lethal study in mice. *In vivo* genotoxicity test	Guideline not stated, purity not stated	Negative	Arnold *et al*. 1974

Table 6. Ecotoxicology profile of diflubenzuron technical concentrate

Species	Test	Duration and conditions	Result	Reference
Daphnia magna	Acute toxicity	48 hr, 20°C, Guideline ASTM E729-80, purity 97.6%	EC_{50} = 2.6-7.1 µg/l NOEC 0.45 µg/l	Kuijpers 1988
Daphnia magna	Acute toxicity	48 hr, 20°C OECD Guideline 202, purity 79.4% (WG, Note 1)	EC_{50} = 3.2 µg WG-80/l NOEC = 0.38 µg WG-80/l	Groeneveld *et al*. 1995
Zebra fish (*Brachydanio rerio*)	Acute toxicity	96 hr, 22°C OECD Guideline 203, purity 95.6%	LC_{50} >0.2 mg/l	Berends & Laan 1994a
Minnow (*Cyprinodon variegates*)	Acute toxicity	96 hr, 22°C Guideline US EPA 40 CFR 158.145 72-3, purity 100% (Note 1)	LC_{50} >130 µg/l	Nicholson 1987
Zebra fish (*Brachydanio rerio*)	Acute toxicity	96 hr, 22°C OECD Guideline 203, purity 79.4% (WG, Note 1)	LC_{50} >106 mg a.i/l	Berends & Laan 1994c
Minnow (*Cyprinodon variegates*)	Acute toxicity	96 hr, 22°C Guideline US EPA FIFRA Subdivision E 72-3 and OECD 203, purity 95.6%	LC_{50} >130 µg a.i./l	Graves & Swigert 1993
Rainbow trout (*Oncorhynchus mykiss*)	Acute toxicity	96 hr, 15°C Guideline OECD 203, purity 95.6% but WG 80 formulation used purity 79.4% (Note 1)	LC_{50} >65 mg/l	Berends & Laan 1994b
Rainbow trout (*Oncorhynchus mykiss*)	Acute toxicity	96 hr, 15°C Guideline OECD 203, purity 79.4% (Note 1)	LC_{50} >106 mg a.i/l	Berends & Laan 1994d
Selenastrum capricornutum (green alga)	Growth rate test	5 days, 22°C Guideline US EPA FIFRA Subdivision J, Series 123-2, purity 95.6%d but WG formulation used (Note 1)	EC_{50} >80 mg a.i./l NOEC = 80 mg a.i./l	Thompson & Swigert 1993
Selenastrum capricornutum (green alga)	Acute toxicity	OECD guideline 201, purity 79.4%	EC_{50} >80 mg a.i./l NOEC = 80 mg a.i./l	Groeneveld *et al*. 1994
Earthworm (*Eisenia fetida)*	Acute toxicity	14 days exposure, 22°C according to OECD guideline 207, purity 95.6%	LC_{50} >780 mg/kg dry soil	Berends *et al*. 1992
Apis mellifera (honey bee)	Acute oral toxicity and field test	Various laboratory, semi-field and field tests under varying conditions. BBA Guideline, purity 79.4% (Note 1).	LD_{50} >100 µg/bee (adults) Dimilin can be applied in the field without affecting honeybee colonies	Kuijpers 1993 Tornier 1995

Species	Test	Duration and conditions	Result	Reference
Bobwhite quail	Acute oral toxicity	Diflubenzuron administered as a single oral exposure by gavage, birds observed for 14 days. No guideline specified, purity 99.4%	LD_{50} >5000 mg/kg bw	Parke 1976a
Mallard duck	Acute oral toxicity	Diflubenzuron administered as a single oral exposure by gavage, birds observed for 14 days. No guideline specified, purity 99.4%	LC_{50} >5000 mg/kg bw	Parke 1976b
Mallard duck	8-day dietary exposure	Birds housed in thermostatically controlled brooders. No guideline specified, purity 100%	LC_{50} >4640 ppm diet (Note 2)	Fink 1973a
Bobwhite quail	8-day exposure	Birds housed in thermostatically controlled brooders. No guideline specified, purity 100%	LC_{50} >4640 ppm diet (Note 2)	Fink 1973b

Note 1: Due to the low solubility of diflubenzuron in water (0.08 mg/l), the acute toxicity was established using Dimilin WG-80 to suspend the active ingredient in water during the test.
Note 2: Highest dose tested.

Diflubenzuron was evaluated by IPCS in 1994 (IPCS 1994) and by the FAO/WHO JMPR for toxicology in 2001 (JMPR 2001) and for residues in 2002 under the periodic review programme of the Codex Committee on Pesticide Residues (JMPR 2002). The 2002 JMPR concluded that the long-term intake of residues of diflubenzuron in food resulting from its uses that have been considered by JMPR is unlikely to present a public health concern. The WHO panel of the 2001 JMPR 2001 that an acute RfD is unnecessary and therefore the 2002 JMPR concluded that the short-term intake of diflubenzuron residues is unlikely to present a public health concern. The 2001 JMPR re-confirmed the previously established ADI of 0-0.02 mg/kg bw.

The WHO hazard classification of diflubenzuron is: unlikely to present acute hazard in normal use (WHO 2002).

Formulations

The main formulation types available are WP (25%), SC (48%, 24%, 22%, 15%), WG (80%), GR (4%), OF (45% and 6%, the latter a ready-to-use formulation) for both agricultural and public hygiene use. Effervescent GR (2%) and DT (2%) formulations are under development and testing for use in public hygiene and submissions have been made for registration of this use.

These formulations are registered and sold in many countries throughout the world. Europe: Austria, Belarus, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Macedonia, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovakia, Spain, Sweden, Switzerland, U.K. Uzbekistan, Yugoslavia. Middle East: Egypt, Iran, Israel, Jordan, Saudi Arabia, Syria, Turkey, United Arab Emirates. Africa: Algeria, Burkina Faso, Cape Verde, Chad, Gambia, Guinea Bissau, Kenya, Madagascar, Mali, Mauritania, Morocco, Niger, Senegal, South Africa, Zimbabwe. Australasia and Asia: Australia, P. R. China, India, Indonesia, Japan, Kazakhstan, Korea South, Kyrgyzstan, Malaysia, Nepal, New Zealand, Pakistan, Taiwan, Thailand. Americas: Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Paraguay, Peru, USA, Uruguay.

Methods of analysis and testing

The analytical method for determination of the active ingredient (including identity tests) in the TK and WP is a full CIPAC method (CIPAC H). Diflubenzuron is determined by reversed-phase HPLC, using a C-18 column and acetonitrile/water mobile phase, with UV detection at 254 nm and linuron as the internal standard. The method has not been validated for GR, WG, OF, SC or DT formulations.

The methods for determination of impurities were based on HPLC-UV, using external standardization.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EPA and EC, while those for the formulations were CIPAC, as indicated in the specifications.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of active ingredient

The active ingredient is expressed as diflubenzuron, in g/kg in solid formulations, and in g/kg or g/l at 20 ± 2ºC in liquid formulations.

Appraisal

The Meeting considered data on diflubenzuron, submitted by Crompton Europe B.V. for the review of existing WHO specifications for the TK and WP. New specifications were considered for diflubenzuron granules (GR) and tablets for direct application (DT) in public health and for suspension concentrates (SC) for use in agriculture. The data submitted were in accordance with the requirements of the manual (FAO/WHO 2002).

Diflubenzuron is a benzoylurea insect growth regulator, used in agriculture, horticulture, forestry and public health applications. It is not under patent.

Diflubenzuron has low solubility in water and is stable in aqueous solution, although its half-life is significantly shorter at higher pH, and it is reasonably stable to photolysis.

The Meeting was provided with confidential information on the manufacturing process and manufacturing specifications for purity and impurities, which were supported by 5-batch analysis data, and a comparison of these data with those submitted for registration in the USA and EU. Mass balances in the 5-batch analyses were high (99.3-100.3%) and no unidentified impurities were detected. A statement was provided by the Australian Pesticides and Veterinary Medicines Authority, confirming that the confidential data on the manufacturing process and declaration of composition (specification limits for the active and impurities) for diflubenzuron provided to the APVMA by Crompton were identical to those provided to the FAO/WHO.

The Meeting agreed that none of the impurities should be regarded as relevant.

Diflubenzuron toxicity was assessed using the relatively pure TC, the TK (VC-90, 90% diflubenzuron), or, for wildlife studies in water, an 80% WG. Diflubenzuron is generally of low acute toxicity and, although a slight reaction was observed in eye irritation tests, this did not warrant its classification as an eye irritant according to EU Directive 67/548/EEC. Diflubenzuron was not observed to cause any carcinogenic, mutagenic, teratogenic or neurotoxic effects. Diflubenzuron is generally of low toxicity to other wildlife, other than insects, with *Daphnia magna* being the most sensitive species reported.

Diflubenzuron was last reviewed by IPCS in 1994 and by the FAO/WHO JMPR in 2001 and 2002. The WHO hazard classification is: unlikely to present acute hazard in normal use.

A full CIPAC analytical method is available for determination and identification of diflubenzuron in the TK and WP. It has not been validated according to CIPAC guidelines for the analysis of GR, DT or SC formulations but it was validated and compared with another method by the manufacturer in a GLP study, in accordance with U.K. PSD guidelines[1]. The two methods are compared in the following table.

	CIPAC Method 339/TK/M/-	GC Laboratories Ltd Method M569
Column	250 x 4.6 mm Zorbax TM_{BP}-C_8 Spherisorb ODS 5 µm	250 x 4.6 mm 4 µm Synergi Polar-RP
Mobile phase	Acetonitrile-water-dioxane (450+450+100 v/v)	Dioxane-water (55+45 v/v)
Flow rate	1.3 ml/min	1.0 ml/min
Column temperature	Ambient	30°C
Detector wavelength	254 nm	254 nm
Injection volume	20 µl	5 µl
Internal standard	Linuron	Diphenyl phthalate
Retention times	Diflubenzuron about 7 min Linuron about 4 min	Diflubenzuron 8.9 min Diphenyl phthalate 12.5 min
Sample solute	Dioxane	Dimethylformamide

Test methods for the determination of physical properties of the TK and formulations are full CIPAC methods.

[1] U.K. Pesticides Safety Directorate. Guidelines for the Validation of Analytical Methods for Pesticides (PRD 2400), Commission Directive 96/46/EC and SANCO/3030/99 rev 4 'Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex III (part A, Section 5) of Directive 91/414'.

The proposed specifications were in accordance with the guidelines given in the manual (FAO/WHO 2002), with the following exceptions.

TK. The Meeting considered whether the specification related to a TC or TK but the manufacturer explained that the TK is a minimally diluted TC, intended for the manufacture of formulations. The nominal content of diflubenzuron in the TK was confirmed to be 900 g/kg, with a tolerance of ±25 g/kg, giving a minimum of 875 g/kg. Additional clauses were proposed for wet sieving, bulk density and particle size distribution. The manufacturer explained that control of particle size is important for good efficacy of the formulations prepared from the TK and the Meeting agreed that a clause for particle size should be included in the specification.

WP. The Meeting questioned the limit of 2 minutes for wettability. The manufacturer explained that this reflected the low affinity of diflubenzuron for water and the Meeting accepted the limit. The manufacturer specified a maximum retention of 1% in the wet sieve test, based on the use of a 44 µm test sieve. The Meeting agreed that the clause should be based on the usual 75 µm test sieve, the manufacturer stated that a limit of 1% would be required and this was accepted by the Meeting.

GR. The Meeting and manufacturer agreed that the term “bulk density” should be replaced by “pour density” and that a clause for pH range was unnecessary. The Meeting agreed that water should be specified as a relevant impurity and that a high limit is required for acidity, after the manufacturer explained that the granules contain an effervescent system, for disintegration of the granules after application to water for insect control. The granules are not intended for dispersion in water prior to application to water in the field and the Meeting agreed that it was not necessary to include a clause for granule disintegration.

DT. The Meeting and manufacturer agreed that a clause for pH range was unnecessary. The Meeting agreed that water should be specified as a relevant impurity and that a high limit is required for acidity, after the manufacturer explained that the tablets contain an effervescent system. The manufacturer explained that the majority of the acid present is not consumed in the effervescent reaction (which aids dispersion of the active ingredient) but, following application of the tablets to water for insect control, also aids dispersal of the active ingredient by simple dissolution. The tablets are not intended for dispersal in water prior to application in the field. Diflubenzuron is a slow-acting insecticide and effects on larvae are generally seen after 24-48 hours. The manufacturer stated that, at water temperatures where mosquito larvae can survive, the tablets fully disintegrate within 10-30 minutes. The Meeting accepted that the high content of water-soluble acid should be sufficient to ensure dispersion, even in the absence of the effervescence reaction, and that therefore it was not necessary to include a clause for tablet disintegration.

SC. The Meeting and manufacturer agreed that a clause for acidity/alkalinity or pH is not required, because diflubenzuron has a very low solubility in water and does not dissociate. The manufacturer proposed a specification for wet sieve testing, based on a maximum retention of 0.1% of the formulation on a 150 µm test sieve. The Meeting agreed that the usual 75 µm test sieve should be specified. The manufacturer stated that tests indicated that maximum residue retention on a 75 µm sieve is less than 1% and the Meeting accepted this as an appropriate limit.

Recommendations

The Meeting recommended that:

(i) existing WHO specifications for diflubenzuron TK and WP should be withdrawn;

(ii) the proposed specification for diflubenzuron TK, as amended, should be adopted by FAO and WHO;

(iii) the proposed specification for diflubenzuron SC, as amended, should be adopted by FAO, subject to CIPAC adoption of the analytical method extension to SC;

(iv) the proposed specification for diflubenzuron WP, as amended, should be adopted by WHO;

(v) the proposed specifications for diflubenzuron GR and DT should be adopted by WHO, subject to CIPAC adoption of the analytical method extensions to these formulations and successful WHOPES testing/evaluation of the GR and DT for public health use.

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